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Structure of Organic Solids at Low Temperature and High Pressure

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This tutorial review looks at structural and supramolecular chemistry of molecular solids under extreme conditions, and introduces the instrumentation and facilities that enable single crystal diffraction studies on molecular crystals at both high pressure and low temperature. The equipment used for crystallography under extreme conditions is explored, particularly pressure cells such as the diamond anvil cell, and their mechanism of action, as well the as cryogenic apparatus which allows materials to be cooled to significantly low temperatures. The review also covers recent advances in the structural chemistry of molecular solids under extreme conditions with an emphasis on the use of singe crystal crystallography in high pressure and low temperature environments to probe polymorphism and supramolecular interactions.

Key Learning Points

- There are a number of major facilities worldwide at which extreme conditions crystallography can be conducted using both X-ray and neutron sources.
- Specialist apparatus is required for high pressure crystallography, particularly the Diamond Anvil Cell.
- Each high pressure technique has different applications, necessary considerations and limitations.
- There are various open flow cryostats and closed cycle refrigerators available to cool samples to extremely low temperatures.
- An increasing range of molecular organic materials of interest to the chemical community have been studied under extreme conditions demonstrating the adaptability of the crystal lattice to the external environment.

Extreme conditions crystallography

The behaviour of materials under extreme conditions, loosely defined as any conditions substantially outside of the ambient environment we live in, has long been of interest to scientists. Laboratory scale experiments under extreme conditions were initially developed by astrophysicists and geoscientists for the purpose of understanding planetary or extra-terrestrial environments. Pressures at the core of Earth reach several million atmospheres, and less accommodating planets and stars have more bizarre conditions still. Early studies focused on the effect of heating, cooling and compression on elemental and mineral composites such as those found in planetary crusts and cores but has since been applied to more complex inorganic systems and organic molecular materials. Achieving extreme conditions in a simulated environment proved difficult in the early days of the science, requiring cumbersome setups impractical for use within conventional university laboratories. Over the last half century, advances in both instrumentation and X-ray diffraction facilities and techniques have allowed high pressure and low temperature studies to develop as a routine method for investigating the structure and properties of a wide variety of materials. Collecting single crystal diffraction data at low temperatures has become standard practice in most laboratories due to advantageous effects such as reduction in thermal motion and diffuse scattering, as well as stabilisation of sensitive samples, which together offer better data quality and ultimately, more precise and accurate crystal structures. With continual improvement in the variety and availability of cooling systems and the accessibility of temperatures close to absolute zero, it is becoming evident that more can be learned from these conditions as materials exhibit new and unusual properties at low temperature. In terms of high pressure studies, the invention of the Diamond Anvil Cell (DAC), more than half a century ago,[1] with its versatile design and ability to reach extremely high pressures (even beyond the pressure region at which most organic solids break down), has revolutionised high pressure crystallography. A key feature is its simple mechanism of action and the fact that the cell can be mounted directly onto a conventional diffractometer *(vide infra)*.[2, 3]

Facilities

Many diffraction studies under extreme conditions require a visit to central facilities because of the specialist nature of the apparatus, and its cost. There are a number of such facilities available around the world. The Diamond synchrotron facility in the UK, for instance, offers DACs for use on the single crystal beam line I19. Both the ESRF (France) and Spring8 (Japan) have dedicated high pressure beam lines for powder diffraction, ID27 and BL10XU. Many neutron source facilities also offer various routes to extreme conditions. ISIS UK, ILL in Grenoble, France, ANSTO in Australia and Oak Ridge Spallation Neutron Source in the USA collectively offer a range of cryostats, closed cycle refrigerators and other specialist cryogenics, providing access to a range of temperatures. In the case of the Oxford Instruments

KelvinoxVT Dilution Refrigerator Insert at ISIS, temperatures as low as 25 mK can be achieved. High pressure neutron studies are less common because of the larger sample size required, however most facilities offer a range of pressure cells for use on their beamlines.

Certain specialist university diffraction laboratories offer access to instrumentation designed for both high pressure (HP) and low temperature (LT) studies on organic molecular crystals.[4] For example, at the Centre for Science at Extreme Conditions based in Edinburgh University, there is a Bruker APEX-II diffractometer complete with Helix He-flow refrigerator capable of taking samples as low as 20 K. For extreme LT work, Copley *et al*. at Durham University developed a four circle single crystal diffractometer for temperatures down to 9 K. This machine consisted of a rotating anode generator, Huber goniometer, Siemens fast scintillations detector and APD '202' Displex cryogenic refrigerator.[5] Several years later Probert *et al.* carried out a rebuild of this system, taking advantage of the more recent developments in equipment rather than altering the existing diffractometer.[4] The LT machine, XIPHOS I, consists of a Mo rotating anode generator with Helios focusing optics, producing a 120 µm beam size at the sample position. A four circle Huber goniometer allows accurate positioning and a modified ^{4}He ILL Joule-Thomson Cryostat permits temperatures as low as 1.9 K to be achieved. It is equipped with a Bruker APEXII CCD area detector. The equivalent machine for high pressure studies, XIPHOS II, consists of a Ag-Kα IµS generator with multi-layer focusing optics.[4]

High pressure crystallography techniques

The Diamond Anvil Cell

High pressure single crystal X-ray crystallography is an expanding area of interest, due in large part to the accessibility of pressures on the order of hundreds of GPa provided by the DAC (Fig. 1A). There is also considerable current interest in the structure of porous materials under much more modest pressures of sorbed gases.[6] The distant ancestor of today's high pressure cells was designed by Bridgman,[7] who used an opposing anvil system initially of chrome steel, and subsequently tungsten carbide cemented in cobalt when the original system proved too brittle.[8] A gasket was used to immobilise the sample under investigation. All of the concepts underlying modern opposing anvil equipment were present, but the leap to opposed anvil diamond cells was not made until 1959, by Jamieson.[2] The general set-up of the diamond anvil cell is shown in Figure 1B. The cell anvils consist of two diamonds, the advantages of which are the low absorption of short wavelength X-rays and transparency to UV, visible and IR radiation as well as the obvious hardness of diamond, allowing the DAC to reach considerable pressures. The first diamonds used in DACs were those confiscated from smugglers by customs agents and donated to research, but the diamonds used these days are rather less exciting synthetic stones.[9]

The diamonds are held in place by a support of brass, steel or tungsten carbide. The sample sits in a small precision drilled hole in a gasket between the culets of the diamonds, with a hydrostatic medium such as paraffin oil or a methanol/ethanol mixture added to ensure isotropic compression. In the sample holder there is also a ruby (5-10 µm), which allows the pressure inside the cell to be measured via a method initially developed by Forman *et al.* in 1972.[10] Rubies fluoresce with a doublet of lines at 692.7 and 694.2 nm at atmospheric pressure. Under pressure, these lines shift linearly to higher wavelength, providing an internal gauge by which the pressure in the cell can be determined.

There are some significant advantages that come with the use of the DAC: namely, high pressures can be achieved, as force is applied over a small area, and the sample can be mounted easily on a normal goniometer due to its compact size. However, there are some limitations to this set-up. The most significant problem is obstruction of the X-ray beam by the support, which limits the range of diffraction angles that may be accessed around the crystal. A partial solution is to use an Ag X-ray source instead of the more conventional Cu and Mo sources. While beam intensity is reduced, more data can be collected within the limited diffraction angle around the crystal, as the smaller wavelength

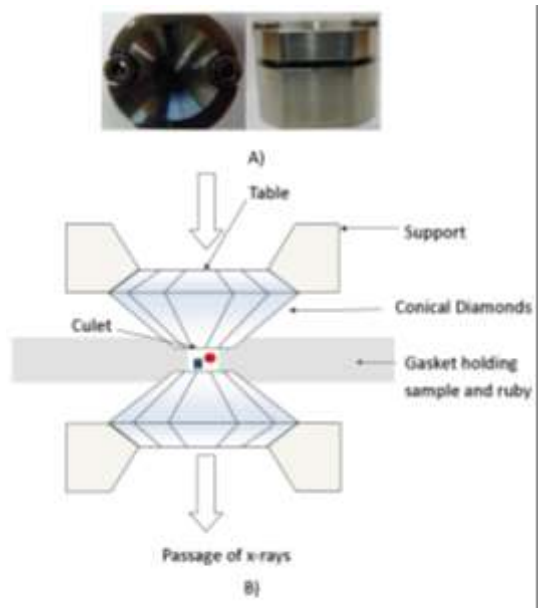

Fig. 1 Diamond Anvil Cell. A) Stainless steel support, showing diamond window. B) Components within the DAC.

(0.56 Å, compared with around 1.54 and 0.71 Å for copper and molybdenum, respectively) means that a greater volume of reciprocal space is accessible as the radius of the limiting sphere is equal to 2/λ. Silver X-ray sources have the additional advantage that the radiation produced is less strongly absorbed by the diamonds of the DAC.

Other disadvantages of DACs include restrictions on the size of the crystal which can be used and the indirect way the pressure has to be measured. The pressure cannot be monitored directly as it is applied, but requires a trial-and-error process to achieve the desired pressure range, particularly when a mechanical screw system is used, although more control may be obtained by use of a gas membrane driven application of pressure. Dawson summarised the problems with data processing caused by DAC collection in 2004.[11] The diffraction pattern of the crystal under study may contain strong reflections from the diamonds, and scattering from the beryllium backing discs which are used in

some versions of the DAC. Some frames may need to be removed from the data set where the detector has been obscured by the body of the DAC, necessitating a manipulation known as dynamic masking.[11] Masking is a correction method applied to shaded areas of the detector such as those created by the beam stop. The beam stop however, does not move relative to the detector, whereas the DAC does, meaning that not one, but a series of masks is needed to account for the various orientations the cell adopts relative to the detector during data collection.

There are a number of absorption and systematic errors which occur when using DACs due to variation of the beam path through the diamonds and shading by the gasket hole. Although acceptable correction can be achieved using only the multi-scan method, as in the program *SADABS*,[12] better data can be gained from a combination of multi-scan and other methods. For example the program *Absorb6.0* written by Angel applies absorption corrections by modelling the absorption profile of the body of the cell and taking into account gasket shadowing and absorption by the pressure media used in the DAC.[13] In addition, one effect which must be dealt with at the integration stage of data processing is the drop in reflection intensity which may be seen in the incident or diffracted beam when the diamond anvils diffract at the same angle as the crystal. These diamond dips must be identified and the affected reflections removed from the data set in order to achieve a sensible integration.

One variation on the DAC involves a miniature diamond anvil cell created at the Centre for Science at Extreme Conditions, at Edinburgh University.[14] This is a 'split-cylinder' design, based on the original Merrill-Bassett cell,[15] and is designed specifically to work with a ^{3}He platform for use in a physical property measurement system (PPMS). The PPMS is designed to have variety of inserts and operates based on a superconductive cryomaget, allowing measurement of properties such as electrical resistivity and magnetic susceptibility. The miniature diamond anvil cell in combination with a ^{3}He insert allows measurements to be obtained up to 10 GPa and down to 0.35 K.

More recently, a version of the DAC was developed which employs a secondary anvil system in the form of two nanocrystalline diamond (NCD) hemispheres mounted directly on to the culets of the primary diamond anvils, allowing pressures above 600 GPa.[16] These NCD micro-spheres are produced by conversion of 20-50 µm carbon glass spheres into NCD using 20 GPa of pressure and a temperature of 2,200 K with a multi-anvil press. Alterations in the synthetic conditions such as pressure media can offer a mixture of forms of NCD, such as spheres and hemispheres of various shapes. Compression of a NCD sphere (coated with a gold film to reduce luminescence) in a typical DAC with a rhenium gasket and neon as the pressure medium was used to test the yield strength of the spheres. The pressure directly above the sphere, close to the culet of the primary diamonds, was measured using Raman spectroscopy of the diamond and the ruby fluorescence method was used to measure the pressure around the sphere in the gasket hole. These two values remain the same until the sphere starts bridging between the primary diamonds (as the gasket thickness reduces with increasing pressure) at which point the pressure at the contact point rapidly increases, with a maximum of 97 GPa at the diamond contact and a corresponding pressure of 41 GPa in the chamber as measured by the ruby chip. The yield stress was subsequently calculated at 144-168 GPa, which is comparable to similar values for single crystal diamond. After confirming that the yield strength and brittleness of the NCD spheres is appropriate, hemispheres were then mounted onto a set of primary diamond anvils as second-stage anvils. The hemispheres must be situated in small cavities carved into the diamond culets by pulsed laser or they will be susceptible to movement on application of pressure, overriding the alignment and affecting the sample environment. Disadvantages to this system are principally due to movement of the secondary anvils out of alignment, which can occur when a cavity is not carved into the primary diamonds, when the NCD hemispheres bridge the primary diamonds at pressures lower than 30-35 GPa (the gasket is too thin) and when the sample is larger than the contact area between the hemispheres.

There are also variations on the DAC in which the cell is miniaturised to achieve higher pressures.[17] However, the standard DAC remains the most commonly used setup for very high pressure work due to its relative simplicity and the considerable pressure range which can be achieved safely.

Details of the DAC

There are several considerations to take into account when selecting or constructing a diamond anvil cell for use:

- The type of diamond
- The shape and size of the diamond.
- The gasket
- Sample hole diameter
- Hydrostatic media
- Pressure determination

Diamond type

Diamond quality is classified based on the type of impurities present and the structural form of these impurities. Type I diamonds for example are the most common yellow diamonds which contain nitrogen impurities.[18] This is sub-categorised into IA, where the impurities are clustered within the carbon structure, and IB where the nitrogen atoms become diffused throughout.[18, 19] Type II white diamonds contain no nitrogen impurities and have lower absorption in the infrared region, but are much more expensive due to their rarity. As a result, low-birefringence Type IA diamonds are the most common anvils and most readily available.

Size and shape

One of the first choices when selecting diamonds for anvils is the cut and size of the diamond. Brilliant cut diamonds are prevalent as this the typical diamond cut used for gemstones and they are therefore readily available. Other designs are also obtainable such as the Drukker Dubbldee design which has a greater table size relative to the culet size (see Figure 1).[19] The shape of the diamond can impact the pressure range accessible, for example the more faces cut into the diamond, the greater stresses it can withstand.

The standard measurement for diamond size is the carat, which is defined as $^1/_5{}^{th}$ of a gram. Diamonds for anvils tend to be of the order of $^1/_3$ or ¼ carat as diamonds any larger than this are more likely to contain flaws which will be exacerbated under pressure

and cause the diamond to crack and no longer be functional as an anvil. There are a range of culet sizes available, and those between 0.5 and 1 mm are typical. The smaller the culet size the greater the pressure that can be obtained.

The gasket

The choice of material for the gasket is largely a question of experimenter preference, although some materials are naturally more compressible than others. Stainless steel is a popular choice, with rhenium being another but more expensive option. The best way to obtain a functional gasket is to purchase sheets thicker than intended for the experiment, and then pre-indent each gasket to the thickness required, before drilling the sample hole.[20] The section of gasket around the sample hole, and the diamonds, are then better supported by the thicker material around the hole. The degree of pre-indentation is important to the success of the experiment; all gaskets will deform by extrusion of the sample hole during an experiment, but the initial thickness of the gasket determines whether this extrusion will be inwards or outwards. If the gasket is thin enough, extrusion occurs inwards, the sample hole becomes smaller, the pressure in the sample chamber increases easily and the hole and diamonds are well supported. In the opposite case, when the gasket is too thick, the sample hole extrudes outwards and becomes larger, the diamonds must be advanced further onto the sample to achieve the same pressure and there is less support from the gasket to the sample chamber. Ideally therefore, the gasket should be pre-indented using close to that pressure which will be applied during the experiment so that it is thin enough around the sample hole.

Sample hole diameter

Ideally, the sample hole radius will be smaller than half of the indentation size, otherwise as the gasket deforms on increasing pressure, the pre-indented material around the sample hole does not adequately support the extruding edge of the hole and thus the pressure within the sample hole will increase less than expected for the force applied to the DAC by the operator. For a more detailed explanation of this effect, see the theoretical discussion by Dunstan.[20] The size of the crystal to be used as well as the culet size of the diamonds must also be taken into account. For poorly diffracting materials, larger crystals will be needed for diffraction, which requires a larger gasket hole and consequently, diamonds with a larger culet size must be used to apply adequate pressure.

Hydrostatic media

In order to obtain a hydrostatically pressurised environment in the sample chamber, an appropriate liquid or gas media must be chosen taking into account the properties of the crystalline sample under study and the pressure range of the experiment. A liquid medium such as a 4:1 methanol-ethanol mixture is the most common and is simple to use.[21] However, if the sample is soluble in either solvent, or the desired pressure is above 10 GPa (the hydrostatic limit of this mixture) another system must be used. In some cases where more stringent conditions for a hydrostatic medium must be met, gases such as argon or nitrogen can be used.

There are two methods of gas loading into DACs, a cryogenic method and a high pressure method. Cryogenic loading requires the DAC to be partially submerged in a cryogen such as liquid nitrogen, which is used to liquefy the gas to be loaded. The DAC is sealed under the liquefied gas, trapping a portion of it in the sample chamber. The alternative high pressure method uses a gas compressor to increase the gas density at ambient temperature which can then be trapped in the DAC by sealing the sample chamber. Table 1 outlines some of the popular choices for hydrostatic media and their limits.[21-23] These values were collected from several publications which use the line widths from ruby fluorescence or diffraction maxima from quartz single crystals to determine the hydrostatic limit.[21]

Table 1. Limits of hydrostatic media

Medium	Hydrostatic limit (GPa)
4:1 Methanol -ethanol	9.8
2-propanol	4.2
Argon	1.9
Nitrogen	3.0
Glycerol	1.4
Silicone oil	0.9
1:1 Pentane-isopentane	7.0
Helium	23
Paraffin oil	3.0

Experimental Pressure Measurement

While ruby is a common choice to provide a route to measurement of the pressure within the DAC, other internal standards such as quartz or sodium chloride may be used provided their equations of state are well known in order to convert the measured unit cell parameters into the corresponding pressures. Any such internal standards are most effective if they are inert in the atmosphere and the chosen hydrostatic medium, and the standard should have a low unit cell volume with high symmetry.[24]

The Quartz Pressure Cell

The Quartz Pressure cell (QPC) uses a quartz capillary to house the crystal during data collection allowing the sample to experience modest gas pressures.[25] This design allows good visual access to the crystal. The capillary can withstand pressures of up to 1 kbar. If a smaller capillary is used, higher pressures can be achieved. Unlike the diamonds in a DAC, quartz creates a halo in the collected frames instead of additional intense Bragg reflections. This makes indexing the crystal considerably more straightforward.

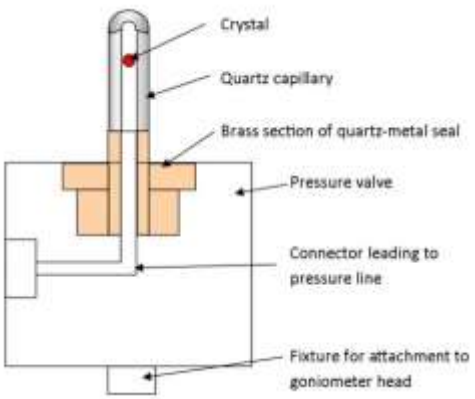

Fig. 2 Schematic of Quartz Pressure Cell

The cell (Fig. 2) generally comprises the quartz capillary which is sealed at one end. The crystal is inserted into the capillary with a small drop of polyfluorinated oil, which is chemically inert, does not dissolve most samples and acts to fix the crystal in place once the oil is cooled. The capillary is mounted directly onto a high pressure valve, and pressurised with a chosen gas using a direct line with a standard gauge attached. Once the cell is pressurised, it is removed from the line and mounted onto the diffractometer. The transparent nature of the quartz allows the crystal to be centred easily, even if it moves initially within the oil during handling. There is currently nothing designed into the QPC to enable direct measurement of the pressure in the capillary, so the accuracy of the experimental value is determined by the reading of the gauge attached to the pressure line.

The procedure used for data collection is to mount the cell directly onto the ω block of the diffractometer. It is only possible to collect the data sets using the ω scan mode using two 180° intervals, but these provide sufficient data, which are indexed separately, and do not require special absorption corrections for the cell.

Another method which utilises capillary crystallisation is the Optical Heating Crystallisation Device (OHCD), which uses a focused IR laser to create a localised crystallisation zone within the capillary. Cycles of irradiation and cooling can be used to produce suitable single crystals in situ on the diffractometer, and this method has been used to obtain crystal structures from materials which are difficult to crystallise under typical conditions, such as gases, ionic liquids and liquid crystals.

The Beryllium Shroud Pressure Cell

In 1988 Tilton designed a high pressure cell for the purpose of studying biomolecules.[26] As biomolecules have significant water content, they are often susceptible to deformation when exposed to air or when pressure is applied anisotropically. Tilton designed a gas loaded pressure cell in which the sample environment can be controlled: the beryllium shroud cell allows isotropic pressurisation of the crystal sample while maintaining an inert atmosphere.

The working part of the cell comprises a beryllium shroud, under which the crystal is mounted on a quartz capillary and support. This is secured to a stainless steel support by a washer and is screwed to a pressure valve. A simplified version of the cell is shown in Figure 3. The sheath is made to a thickness which can withstand 400 atm. Once sealed, pressurised, and removed from the gas source, the fixture maintains its internal pressure for up to a month. Centring of the crystal is managed optically before pressurisation and can later be optimised using diffraction. A control experiment was carried out by Tilton with and without the beryllium shroud and no significant difference was found between the two sets of data. Although the cell is sufficient for data collection at pressures up to 400 bar, it exhibits a number of disadvantages. The crystal is not visible once the assembly is put together resulting in extra steps being required to centre the crystal accurately. In addition, the weight of the cell causes positioning errors, and shading of the detector by the stainless steel support limits data collection to the $-\chi$ and $+\theta$ directions. The nature of the cell also raises some safety issues. Beryllium is toxic, and repeated pressurisation cycles and corrosion by organic salts can cause micro-pitting and cracks in the shroud. Coupled with the application of high gas pressures to the cell, damage to the shroud can cause the shroud to rupture, presenting a significant safety hazard.

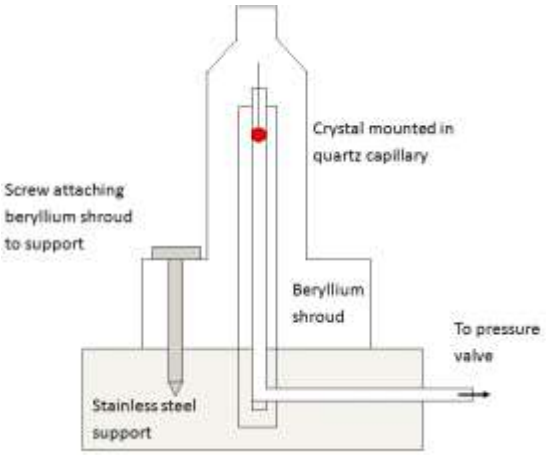

Fig. 3 Schematic of Tilton's Beryllium Shroud Pressure Cell.[26]

The Paris-Edinburgh Cell for neutron diffraction

The Paris-Edinburgh Cell (PEC) cell was designed specifically for powder neutron diffraction at the ISIS neutron source, UK.[27] Like the DAC it operates an opposed anvil design, but tungsten carbide makes up the anvil, and the sample environment is a sphere approximately 100 mm^3 in volume, supported by a gasket of pyrophyllite and beryllium copper. The anvils are supported by steel binding rings, which are partially hollowed out in the direction which the neutron beam will follow to reduce absorption. To provide adequate force to achieve high pressures within the cell, a 250 tonne press was built to accompany the PEC utilising a hydraulic ram which allows variation of the pressure *in situ* (Figure 4).

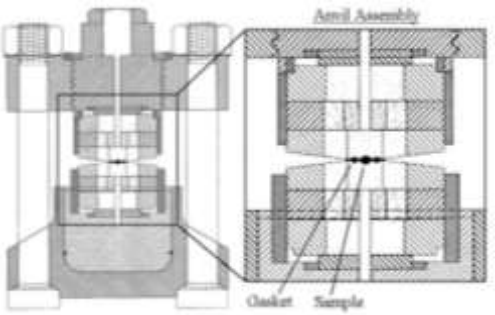

Fig. 4. Complete Paris Edinburgh Cell, including hydraulic ram with the anvil and sample environment highlighted on the right.[27]

The ZAP cell for neutron diffraction

Building on the concept of a high pressure cell specifically designed for neutron diffraction, Zhao *et al*. developed the ZAP

cell, an opposed anvil cell with structural similarities to the DAC and PEC.[28] The anvils consist of single crystal moissonite mounted on piston cylinders and the pressure is loaded using a hydraulic press. The gasket used is either aluminium or TiZr. The cylindrical windows of the cell allow a greater volume of real space around the sample to be accessed, compared to the PEC, an essential feature for the relatively low intensity incident neutron beam. Pressures up to 20 GPa have been achieved with this cell.

Low temperature crystallography

Introduction

Low-temperature (LT) X-ray crystallography techniques were developed for the purpose of minimising radiation damage to single-crystal specimens as well as reducing thermal motion within the crystal lattice.[3] LT conditions reduce interference caused by thermal diffuse scattering within the crystal. Now, with temperatures approaching absolute zero becoming attainable, LT crystallography may provide access to a new realm of structural investigation, allowing temperature-dependent properties to be probed in unprecedented detail.

Open Flow Gas Cryostats

Nitrogen based cryostats

Open flow nitrogen gas cryostats (OFNCs) are the standard instrumentation for single crystal diffractometers in most modern crystallography laboratories. An ONFC can produce temperatures as low as 80 K, but operating temperatures in the range 120-150 K are typical.[4] The major advantage of open flow cryostats is that they do not require a closed system in order to cool a sample effectively, so the crystal can be accessed easily However, in older versions of these cryostats, it is difficult to precisely maintain the temperature of the sample. The general set up of a modern OFNC overcomes this issue and is detailed in Figure 5.[29]

Liquid nitrogen is drawn directly from the unpressurised Dewar vessel (a), through a vacuum-insulated pipe (b). The liquid flows into a high vacuum insulated chamber where it passes through a heating coil (c) and heat exchanger, resulting in vaporisation. Flowing out of the chamber, the gas flow passes through a needle valve (d) which regulates the gas flow rate, and

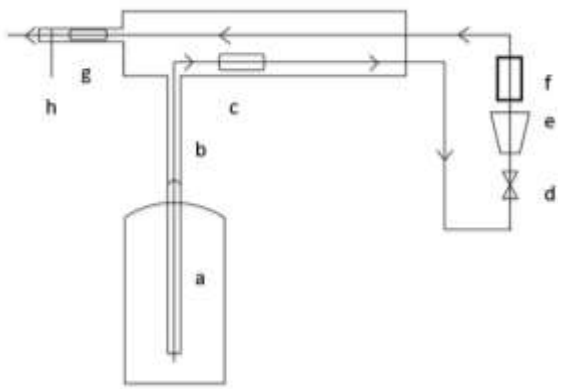

Fig. 5 Open flow nitrogen gas cryostat.[29]

arrives at the diaphragm pump (e). The gas is re-cooled as it passes through the other side of the heat exchanger. It then passes over a second heating coil (g) and thermal sensor before arriving at the sample.

Helium based cryostat

Following the development of the OFNC, a cooling system based on helium represents a natural progression. Open flow helium gas cryostats (OFHCs), such as the N-Helix systems (available from Oxford Cryosystems), can deliver significantly lower operating temperatures, so there are the preferred cooling method for high-accuracy LT structure determination below 80 K.[30]

One of the first OFHCs, designed by Moffat and co-workers, was a custom built two-part setup which allows the experimenter to switch between using nitrogen or helium gas depending on the desired temperature (80 K for nitrogen, 10-70 K for helium).[31] In an attempt to improve the accessibility of helium cryostats, Hardie and co-workers described the assembly of an open flow system from an ESR helium cryostat and other, readily available components.[32] Both the Moffat and Hardie systems can be used in diffraction studies without limiting the visibility or accessibility of the crystal during alignment and data collection. However, the use of OFHCs in LT crystallography has so far been limited, due to their rapid consumption of an expensive cryogen. In the Hardie system, cooling to 20 K requires a helium flow of 4 L h^{-1}, and cooling to 14 K demands greater volumes still. Although these consumption rates are an improvement to those achieved by the Moffat group, they are still too large for helium-cooling to be widely adopted in the crystallographic community. One successful application by the Howard and Yaghi groups used a Helix OFHC to cool MOFs to temperatures between 30 and 293 K, showing that the occupancy of various gas sites within the MOF structure is temperature dependent.[33]

Closed cycle refrigerators (CCRs) require a much smaller volume of helium gas, as they operate by compression, expansion and recycling of the gas, which in turn is in thermal contact with the sample.[3] One such system, the closed-cycle two-stage helium refrigerator, allows cooling to temperatures as low as 9 K.[5] A common disadvantage of CCRs is that the crystal must be housed in a shroud, similar to in the design of the beryllium shroud pressure cell resulting in longer cooling times, significant background scattering and no possibility of viewing the sample once enclosed. This shroud is commonly composed of beryllium but in the case of neutron systems, aluminium is used.

Similar to data integration from DAC X-ray studies, CCRs necessitate the generation of masks due to the scattering from the beryllium shrouds. Although beryllium is largely transparent to X-rays, the effect is significant enough that a program is required to calculate the appropriate masks. Such a program is '*Masquerade'* which uses the known position of the shrouds and the simulated diffraction pattern of beryllium to determine where scattering from beryllium will occur on the overall diffraction pattern, and the appropriate corrections are made.[34]

Structure of Molecular Crystals under Extreme Conditions

While all crystalline solids exhibit some structural variation in response to changes in their environment, this variation can take many different forms. In high pressure studies, particularly those

involving DACs, materials can be manipulated in more than one way. Compression can be used to crystallise substances which are liquid at ambient conditions. This may prove particularly useful if the substance is difficult to crystallise or has metastable forms which are difficult to isolate at ambient conditions. DACs can also be used to compress an existing single crystal of appropriate dimensions. Any of these methods can cause the sample to exhibit changes in its crystal structure.[35] Of significant interest are pressure-induced phase changes resulting in the discovery of new polymorphic forms, for example. Alternatively, the material may exhibit smaller structural changes; compression may occur anisotropically in one or two dimensions, accompanied by changes to the unit cell parameters and/or molecular conformation.

In certain cases, a structure may undergo significant structural changes at low temperature beyond reduction in disorder and thermal motion; two of the chief motivations conducting crystallography at low temperature. As with high pressure, low temperature may reveal phase changes or allow the formation of crystals or co-crystals which do not exist at ambient conditions.

The QPC and Beryllium pressure cell

Barbour has shown how the QPC may be used to facilitate *in situ* X-ray diffraction studies of gas loading in a metallocyclic host.[6] The macrocycle consists of the ligand 4,4'-bis(2-methylimidazole-1-ylmethyl) biphenyl (**1**) and $CdCl_2$ units, and contains a cavity capable of accommodating two guest molecules of the appropriate size, such as methanol (Figure 6).

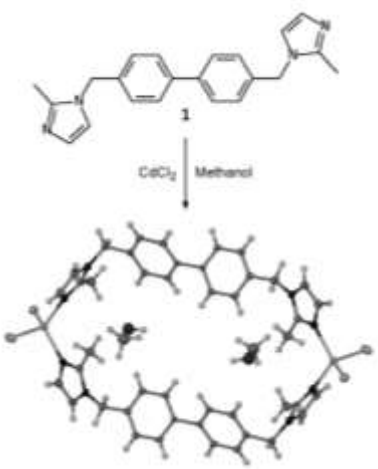

Fig. 6 Structure of ligand **1**and one metallocycle with two methanol guests, $[Cd_2Cl_4\mathbf{1}_2].2CH_3OH$

The macrocycles stack into columns in the extended crystal structure, with their cavities aligned to form a one-dimensional pore. In their study, the Barbour group replaced the guest methanol molecules with the similarly sized gaseous probes CO_2 and C_2H_2. It was found that the metallocycle is fully occupied with CO_2 molecules at 10 bar and -40°C, whereas two C_2H_2 molecules are present in each cavity at 16 bar and ambient temperature. For C_2H_2, the cavities are singly occupied at 2 bar, and the guest molecule must undergo an orientational change before a second guest can be accommodated. The gas loaded crystals are not stable at ambient conditions and experience spontaneous loss of the guest. Thus, it was essential in this study that the apparatus used for gas loading could also serve as a high pressure cell for diffraction studies.

Beryllium pressure cells have been used in particular in protein crystallography, as they offer a suitable route to maintain the protein crystals in a fixed environment as well as a pressurised one. Proteins are susceptible to conformational change when exposed to the atmosphere, as a large proportion of their mass is water, which is easily lost when the protein crystal is no longer in its mother-liquor. Tilton showed that the beryllium pressure cell can help overcome this difficultly as in a trial diffraction experiment, the beryllium shroud pressure cell was applied successfully to the structural analysis of sperm-whale myoglobin at 145 atm.[26] In addition to enabling constant pressurisation, the cell permitted the use of a pre-hydrated nitrogen atmosphere, such that dehydration of the crystal could be prevented.

In addition to pre-hydrated inert gases, an atmosphere of the heavier noble gases can be applied to protein crystals using the beryllium cell. This is a technique used in protein crystallography to derivatise proteins allowing multi-wavelength anomalous dispersion studies. Both a 17 kDa Fe protein myoglobin form sperm whale and an 18 kDa protein from green abalone have been successfully derivatised with Kr gas using pressures of 2.76 MPa applied with a beryllium cell.[36]

The DAC

Urea has a number of known polymorphs and co-crystals. The common ambient form phase I (or α form) has a tetragonal structure in space group $P\bar{4}2_1m$ with hydrogen bonding in a $R_2^1(6)$ motif or "urea α-tape".[37] From crystals grown in a DAC, it is evident that a phase transition at 0.48 GPa yields the γ form (the β phase typically refers to the inclusion compound phase of urea) with space group $P2_12_12_1$ and $Z = 4$. Further increasing the pressure to 2.8 GPa results in another transition to the δ form, which also falls in the space group $P2_12_12_1$ with $Z = 2$. In the α form, the carbonyl oxygen atom forms four hydrogen bonds to atoms on three individual neighbouring molecules. This arrangement is similar to the bonding seen in the δ phase, which can be considered a compressed version of the ambient α form, in which the *a* axis is shortened by 2.16 Å and the *b* axis elongated by 1.77 Å (Figure 7). In both structures, each molecule forms 8 hydrogen bonds to its neighbours in total.

The γ phase occurs as an intermediate between the α and δ polymorphs and exhibits a distinctly different structure, with each carbonyl oxygen atom forming only three hydrogen bonds. Also, in comparison to the other polymorphs, the orientations of the molecules appear significantly altered.

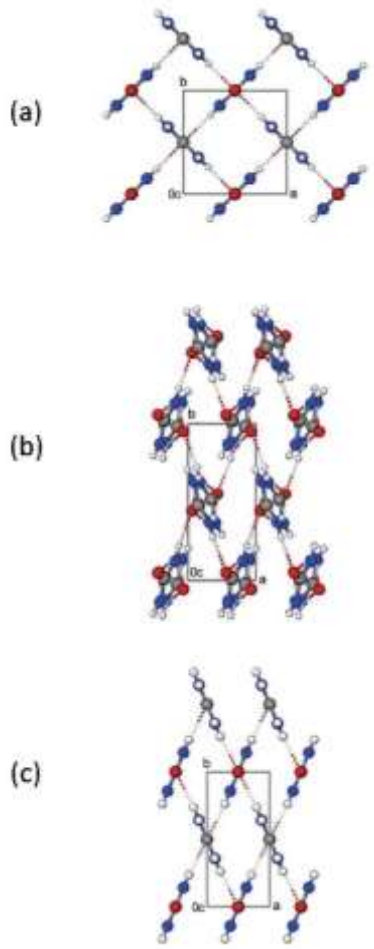

Fig. 7. Ambient and high pressure phases of urea; (a) α-phase $P\bar{4}2_1m$ (b) γ-phase $P2_12_12_1$ (c) δ-phase $P2_12_12_1$

The natural amino acids also display marked phase transitions as a result of elevated pressures. Glycine, the simplest of the amino acids, has three ambient polymorphs labelled α, β and γ. These are crystallised from different solvent systems but all comprise zwitterionic glycine molecules linked by NH···O hydrogen bonds between the ammonium and carboxylate groups. The hydrogen-bonded molecules form one-dimensional chains, which are differently aligned in each of the three ambient polymorphs.[38] α-glycine has been pressurised in increments up to 6.2 GPa with no change observed in its structure except for an increase in the efficiency of the crystal packing. This is consistent with data from Raman spectroscopy which indicates that the structure of α-glycine persists up to pressures of 23 GPa. On the other hand, β-glycine undergoes a reversible single-crystal-to-single-crystal transition at 0.8 GPa to a δ form, despite structural similarities to the non-responsive α form under ambient conditions. At ambient conditions, γ-glycine differs from the other forms as it crystallises in the chiral space groups $P3_1$ and $P3_2$ and the hydrogen bonded chains arrange in a 3_1 screw axis rather than in layers. For this polymorph, a transition to ε-glycine is seen between 2 and 4.3 GPa with a mixture of the two forms occurring at intermediate pressures, although this is not a single crystal transition and results in a polycrystalline sample. Like other forms, ε-glycine has a layered structure. Interestingly, on lowering the temperature, ε-glycine does not immediately convert back to the γ form but instead goes through an unstable intermediate called the ζ phase. The structure of this phase has not been determined due to its short lifetime.

Other amino acids, such as serine, leucine and alanine, also show polymorphism under both ambient and extreme conditions.[38] Cysteine for example, which has two ambient forms, shows a decrease of 8.6% in the length of the *a*-axis on compression of form I to 1.8 GPa, essentially closing up gaps in the extended structure as rows of molecules shift along the *c*-axis. Upon further compression, a single-crystal-to-single-crystal transition occurs to a third phase, cysteine-III, during which the orientation of the sulfur-containing side-chain changes. On release of compression, cysteine-III is converted to cysteine-I via an intermediate, cysteine-IV, which is not seen during the pressure increase. Serine also shows two phase transitions under pressure, at 5.2 and 8.0 GPa, characterised by changes in the hydrogen bonds formed by the hydroxyl group.

Biomolecules other than amino acids are also susceptible to structural changes on the application of pressure. For example, the DNA fragments $d(GGTATACC)_2$ and $d(CGCGAATTCGCG)_2$ have both been studied at pressures up to 2 GPa.[39] The first of these crystallises in space group $P6_1$ with six molecules in the unit cell. This molecule shows a decrease in cell volume up to 1.5 GPa but after this, displays negative compressibility as the pressure continues to increase. Diffraction from this DNA sequence stops above pressures of 2 GPa. Compressibility of the DNA is greatest in the direction of the double helix axis and relatively small in the other directions. The dodecamer, which crystallises in space group $P2_12_12_1$, is less stable to pressure and diffraction is lost above 0.7-0.8 GPa. The structure shows 1.9% compression in terms of unit cell volume at 0.3 GPa, with the same pattern of compression along the double helix.

Ridout *et al*. investigated the high pressure crystallisation and polymorphism of a series of fluorotoluenes that are liquid under ambient conditions and found that both 3- and 4-fluorotoluene exhibit polymorphism under extreme conditions of temperature and pressure.[40] 3-Fluorotoluene exhibits two forms: one in the space group $P2_1/n$ (the LT form obtained at ambient pressure at 179 K) and another in *Pbca* (the HP form obtained at 10 kbar) The structural difference between the two is immediately evident on inspection (Figure 8). The HP structure is based on an ABCDABCD repeating pattern in one dimension, while the LT structure displays the same motif in two dimensions. The hydrogen-bonding pattern between layers is different in each form, with the length of the C-H···F-C hydrogen bond changing from 2.682(3) Å (LT) to 2.441(3) Å (HP). Similarly, 4-fluorotoluene has a polymorph I (LT) in the space group $P2_1/c$, which converts under compression to polymorph II (HP), in the space group *Pnma* Interestingly, the high-pressure polymorph exhibits longer hydrogen bond lengths (2.832(2) as opposed to 2.589(3) Å) despite its higher crystal density (1.290 g cm^{-3} compared with 1.150 g cm^{-3}). This polymorphism is likely the

result of the relative weakening of C-H···F-C interactions at high pressures: the structure-directing effect of the hydrogen bonds is lost and maximisation of packing efficiency dictates the structure.

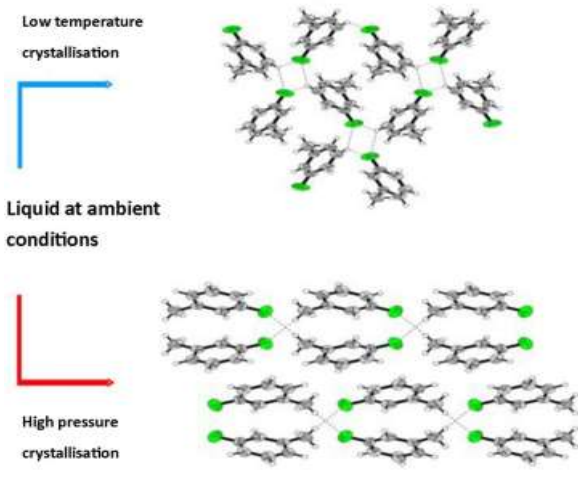

Fig. 8. The HP and LT forms of 3-fluorotoluene.[40]

Pyrazole offers another example of an organic hydrogen bonded structure which exhibits both temperature and pressure dependency with regards to not only its structure but also its ferroelasticity.[41] The ambient phase of pyrazole crystallises in space group $Pna2_1$ with NH···N bonds creating double loop helices. The protons are ordered within these hydrogen bonds. Interestingly, on changes in temperature, disproportionation of the molecules occurs, showing a temperature dependent ionic disparity, as the protons in the NH···N hydrogen bonds become disordered, resulting in partial charges on each pyrazole. It seems in this case, temperature alone is sufficient to introduce a neutral to ionic transition which is somewhat atypical between molecules of the same compound. On average, the charge of the cations and anions is +0.1 and -0.1 e respectively and in general, increases on increasing temperature although some fluctuation occurs. In addition to this temperature induced effect, the structure of pyrazole undergoes a phase transition above a pressure of 0.45 GPa at 296 K to a centrosymmetric phase β, similar to the α phase but of higher symmetry in space group *Pnab* (Figure. 9).

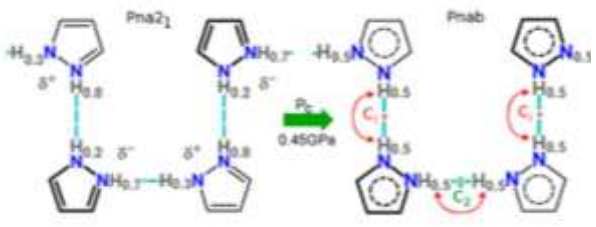

Fig. 9 The phases of pyrazole showing partial charges and symmetry relationships present in the hydrogen bonding 'loop'.

Hydroquinone is an example of an inclusion compound which exhibits a different crystal form under pressures exceeding ~20MPa.[42] At ambient pressure and temperature, hydroquinone has three forms: the clathrate-forming α and β and a more densely packed form, γ, which is accessible only *via* sublimation. The β and γ forms both spontaneously transform to the α form, the most stable phase at room temperature. At 20 MPa and 432.1 K, the system undergoes a phase transition from the α form to a new δ form, demonstrated by Differential Thermal Analysis plots. At temperatures above or below 432.1 K, however, the pressure must be up to 90 MPa for the phase transition to occur. Unfortunately, the conditions under which the δ phase exists have not been recreated on a diffractometer so the crystal structure has not been determined. Nonetheless, using the crystal densities and intermolecular potential, it has been concluded that the δ form may be similar to the γ form, in the monoclinic space group $P2_1/c$ and exhibiting 4 molecules in its unit cell.

Johnstone *et al.* studied single crystals of salicylamide at ambient pressures and up to 5.1 GPa with a DAC. Structural changes were investigated both by compressing an existing single crystal and by growing crystals *in situ*.[43] Salicylamide crystallises under ambient conditions in the space group *I*2/*a* and the hydrogen bonding pattern effectively gives planar dimerization of the molecules, which then form an open network via π···π stacking interactions. On compression to 5.1 GPa, an anisotropic change is seen in the unit cell parameters the *c*-axis decreases by 14.5%, as well as a 4.7% and 4.1% decrease in the *a* and *b* axes, respectively. The effect of this change is to push the layers of hydrogen bonded molecules closer together. *In situ* crystallisation of salicylamide at 0.2 GPa results in another polymorph, (in the Sohncke space group $P2_12_12_1$). similar to that found at ambient conditions but with a twist in the amide group that leads to a change in torsional angle of 4.1°. As a result of the altered amide conformation, the molecules no longer form dimers, but still exhibit two intermolecular hydrogen bonds with the same donor-acceptor pairing.

High pressure diffraction can be used as a tool for investigating the effect of pressure on active pharmaceutical ingredients (APIs) such as paracetamol. A material may be analysed under compression to screen for polymorphic transitions or investigate the effect of tableting process on the crystal structure. For example, DAC studies were used by Boldyreva *et al.* to study the structures of the monoclinic (Form I) and orthorhombic (Form II) forms of paracetamol, upon compression to 4.5 GPa and 5.5 GPa respectively.[44] The bulk compressibilities of the two forms are similar, but the systems display differing anisotropy in their pressure-induced structural changes. Form II exhibits a contraction in three dimensions while form I displays some expansion above 1.5 GPa. No polymorphic transitions have been observed for either form up to 4.5 GPa on increasing and decreasing the pressure.

Methanol is a representative example of a substance which exhibits polymorphism as a result of changes in both temperature and pressure. On cooling, methanol freezes at 175.37 K, giving the 'high temperature' β phase ($Cmc2_1$) which undergoes a first order phase transition to the lower temperature α phase ($P2_12_12_1$) at 156-159 K.[45] There is debate as to whether there is a second, second-order phase transition between 156 and 159 K, but no structural information has been reported for this elusive phase.[46] Methanol also has a third structure in $P\bar{1}$, which is made evident not by temperature but by increasing the pressure on a single

crystal. This was done in a DAC by increasing the pressure above 7 GPa to give a number of crystallites, then reducing the pressure until one seed crystal remained which was subsequently grown to fill the gasket hole at 4.0(1) GPa.[47]

Low temperature can not only enable crystals to be obtained which do not exist at ambient conditions, but also may reveal polymorphism of a substance. An example of both these outcomes is given by diphenyl ether.[48] The crystal structure of this organic solvent had not been solved previously but *in situ* cryo-crystallisation allowed a suitable single crystal to be grown in order to obtain a structure in monoclinic space group $P2_1/n$ at 250 K (Figure 10). It was then found that at only 10 K difference, at 240 K, a second orthorhombic form exists in $P2_12_12_1$. Both crystallisations were achieved by flash-freezing with N_2 gas and then cycling the temperature until a single crystal was obtained.

There is a small conformational change seen in the diphenyl ether molecule itself with angles between the phenyl ring planes of 88.4° and 87.6° for forms I and II respectively. The largest contribution to the structural change comes from the CH···π interactions. In form one, a three dimensional network is formed with chains of molecules along the *a* axis which link to form the larger structure. For form II however, CH···π interactions cause the molecules to form tetramers, which then stack into the extended structure via CH···O interactions. The exact temperature at which this phase change occurs is not reported.

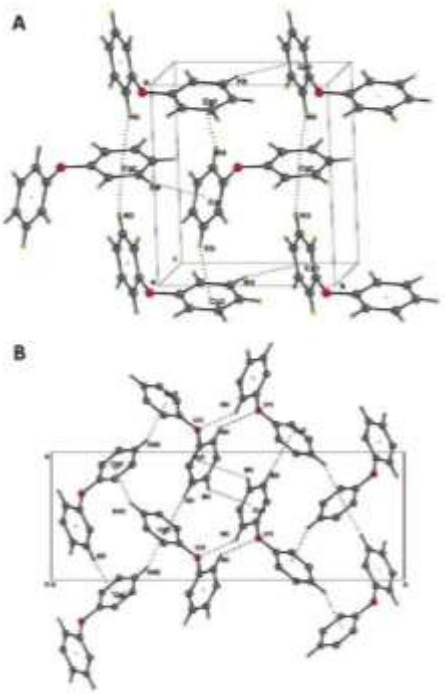

Fig. 10. Polymorphs of diphenyl ether. A) Form I $P2_1/n$ (250 K). B) Form II $P2_12_12_1$ (240 K).

A more complex structure which is affected by external pressure is the 'magnetic sponge' $\{[Mn^{II}(pydz)(H_2O)_2][Mn^{II}(H_2O)_2][Nb^{IV}(CN)_8].3H_2O\}_n$ (**2**).[49] At ambient conditions, this compound crystallises from aqueous solution in space group $P2_1/c$ into a three dimensional grid system with Nb centres and Mn-NC-Nb ladder motifs. Of the eight CN ligands surrounding the niobium centres, seven of them are bridging to manganese ions, with the magnetic moments of the metal centres aligned anti-parallel, causing the material to be a soft ferrimagnet below the critical temperature T_c of 43.5 K. The Nb-C bonds of the bridges are the main structural feature affected by the application of pressure. At 1.8 GPa in a DAC, the structure of **2** is similar to the ambient pressure structure but the unit cell has been compressed by ~7.6 % in volume, with shortening of the Nb-C bonds. This is presumed to be the reason for changes in the value of T_c which are seen with increasing pressure. At pressures 0.57, 0.27 and 0.0 GPa, T_c has values of 51.0, 48.0 and 43.5 K respectively. This indicates that the antiferromagnitc coupling between Mn and Nb via the Nb–CN–Mn bonds is enhanced as the bridge bond shortens with increasing pressure, improving the exchange of spin density between the relevant magnetic orbitals on the metals.

It is becoming evident as research into high pressure crystallography increases that certain crystal forms are only accessible when crystallised in situ at high pressures. One such crystal form is the heptahydrate of gabapentin, a γ-amino acid which is a Pfizer product prescribed for the treatment of epilepsy.[50] At ambient pressure, gabapentin has three polymorphs as well as a monohydrate and a hemihydrate hydrochloride salt. The crystals were grown from a saturated aqueous solution of gabapentin in a diamond anvil cell. On precipitation of a number of crystallites at 0.8 GPa, temperature control was used to isolate a single crystallite which was subsequently grown to a suitable size for diffraction. This method was repeated and two crystals were used to collect data, at pressures of 0.87 and 0.90 GPa. The gabapentin in this structure is in its zwitterionic state, and is high dipolar and as such the structure as a whole consists primarily of alternating columns of polar and non-polar interactions. These two molecule-thick columns have a parallel/anti-parallel arrangement with regards to dipole orientation, and this is also seen in the monohydrate form of gabapentin.

Conclusions

Although there are an increasing number of examples of structure variation under extreme conditions, application of very high pressure or very low temperatures is still a largely untapped resource when it comes to fully exploring the structural and bonding possibilities of molecular materials. As instrumentation and methodology consistently improve, it is becoming ever easier to access this previously inaccessible realm outside the niche conditions we inhabit. We are learning more about materials that were once thought to be fully understood, and there is much scope for improvement in the investigation into molecular and supramolecular systems.

Notes and references

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1. W. A. Bassett, *High Pressure Res.*, 2009, **29**.
2. J. C. Jamieson, A. W. Lawson and N. D. Nachtrieb, *Rev. Sci. Instrum.*, 1959, **30**, 1016-1019.
3. A. E. Goeta and J. A. K. Howard, *Chem. Soc. Rev.*, 2004, **33**, 490-500.
4. M. R. Probert, C. M. Robertson, J. A. Coome, J. A. K. Howard, B. C. Michell and A. E. Goeta, *J. Appl. Crystallogr.*, 2010, **43**, 1415-1418.
5. R. C. B. Copley, A. E. Goeta, C. W. Lehmann, J. C. Cole, D. S. Yufit, J. A. K. Howard and J. M. Archer, *J. Appl. Crystallogr.*, 1997, **30**, 413-417.
6. T. Jacobs, G. O. Lloyd, J.-A. Gertenbach, K. K. Müller-Nedebock, C. Esterhuysen and L. J. Barbour, *Angew. Chem.-Int. Edit.*, 2012, **51**, 4913-4916.
7. R. J. Hemley, *High Pressure Res.*, 2010, **30**.
8. P. W. Bridgman, *Proc. R. Soc. Lond. A*, 1950, **203**, 1-17.
9. G. J. Piermarini, *J. Res. Natl Inst. Stand. Technol.*, 2001, **106**.
10. R. A. Forman, G. J. Piermarini, J. D. Barnett and S. Block, *Science*, 1972, **176**, 2.
11. A. Dawson, D. R. Allan, S. Parsons and M. Ruf, *J. Appl. Crystallogr.*, 2004, **37**, 410-416.
12. G. M. Sheldrick, University of Göttingen, Germany, 2004.
13. R. Angel, *J. Appl. Crystallogr.*, 2004, **37**, 486-492.
14. K. V. Kamenev, J. Sanchez-Benitez and S. Tancharakorn, *High Pressure Res.*, 2007, **27**, 189-192.
15. L. Merrill and W. A. Bassett, *Rev. Sci. Instrum.*, 1974, **45**, 290-294.
16. L. Dubrovinsky, N. Dubrovinskaia, V. B. Prakapenka and A. M. Abakumov, *Nat. Commun.*, 2012, **3**, 2160/2161-2160/2167.
17. E. Sterer, M. P. Pasternak and R. D. Taylor, *Rev. Sci. Instrum.*, 1990, **61**, 1117-1119.
18. C. M. Breeding and J. E. Shingley, *Gems & Gemology*, 2009, **45**, 15.
19. D. J. Dunstan and I. L. Spain, *J. Phys. E: Sci. Instrum.*, 1989, **22**, 913-923.
20. D. J. Dunstan, *Rev. Sci. Instrum.*, 1989, **60**, 3789-3795.
21. R. J. Angel, M. Bujak, J. Zhao, G. D. Gatta and S. D. Jacobsen, *J. Appl. Crystallogr.*, 2007, **40**, 26-32.
22. S. Klotz, J.-C. Chervin, P. Munsch and G. L. Marchand, *J. Phys. D: Appl. Phys.*, 2009, **42**, 075413.
23. G. J. Piermarini, S. Block and J. D. Barnett, *J. Appl. Phys.*, 1973, **44**, 5377-5382.
24. R. J. Angel, D. R. Allan, R. Miletich and L. W. Finger, *J. Appl. Crystallogr.*, 1997, **30**, 461-466.
25. D. S. Yufit and J. A. K. Howard, *J. Appl. Crystallogr.*, 2005, **38**, 583-586.
26. R. F. Tilton, *J. Appl. Crystallogr.*, 1988, **21**, 4-10.
27. J. M. Besson, R. J. Nelmes, G. Hamel, J. S. Loveday, G. Weill and S. Hull, *Physica B: Condensed Matter*, 1992, **180–181, Part 2**, 907-910.
28. Y. Zhao, J. Zhang, H. Xu, K. Lokshin, D. He, J. Qian, C. Pantea, L. Daemen, S. Vogel, Y. Ding and J. Xu, *Appl. Phys. A*, 2010, **99**, 585-599.
29. J. Cosier and A. M. Glazer, *J. Appl. Crystallogr.*, 1986, **19**, 105-107.
30. A. E. Goeta, L. K. Thompson, C. L. Sheppard, S. S. Tandon, C. W. Lehmann, J. Cosier, C. Webster and J. A. K. Howard, *Acta Crystallogr. Sect. C-Cryst. Struct. Commun.*, 1999, **55**, 1243-1246.
31. T. Teng, W. Schildkamp, P. Dolmer and K. Moffat, *J. Appl. Crystallogr.*, 1994, **27**.
32. M. J. Hardie, K. Kirschbaum, A. Martin and A. A. Pinkerton, *J. Appl. Crystallogr.*, 1998, **31**, 815-817.
33. J. L. C. Rowsell, E. C. Spencer, J. Eckert, J. A. K. Howard and O. M. Yaghi, *Science*, 2005, **309**, 1350-1354.
34. J. A. Coome, A. E. Goeta, J. A. K. Howard and M. R. Probert, *J. Appl. Crystallogr.*, 2012, **45**, 292-298.
35. E. Boldyreva, *Acta Crystallogr. Sect. A*, 2008, **64**, 218-231.
36. A. Cohen, P. Ellis, N. Kresge and S. M. Soltis, *Acta Crystallogr. Sect. D-Biol. Crystallogr.*, 2001, **57**, 233-238.
37. A. Olejniczak, K. Ostrowska and A. Katrusiak, *J. Phys. Chem. C*, 2009, **113**, 15761-15767.
38. S. A. Moggach, S. Parsons and P. A. Wood, *Crystallogr. Rev.*, 2008, **14**, 143-184.
39. I. Ascone, R. Kahn, E. Girard, T. Prange, A.-C. Dhaussy, M. Mezouar, N. Ponikwicki and R. Fourme, *J. Appl. Crystallogr.*, 2010, **43**, 407-416.
40. J. Ridout and M. R. Probert, *Cryst. Growth Des.*, 2013, **13**, 1943-1948.
41. M. Sikora and A. Katrusiak, *J Phys. Chem. C*, 2013, **117**, 10661-10668.
42. M. Naoki, T. Yoshizawa, N. Fukushima, M. Ogiso and M. Yoshino, *J. Phys. Chem. B*, 1999, **103**, 6309-6313.
43. R. D. L. Johnstone, A. R. Lennie, S. F. Parker, S. Parsons, E. Pidcock, P. R. Richardson, J. E. Warren and P. A. Wood, *CrystEngComm*, 2010, **12**, 1065-1078.
44. E. V. Boldyreva, T. P. Shakhtshneider, H. Ahsbahs, H. Sowa and H. Uchtmann, *J. Therm. Anal. Calorim.*, 2002, **68**, 437-452.
45. M. T. Kirchner, D. Das and R. Boese, *Cryst. Growth Des.*, 2008, **8**, 763-765.
46. B. H. Torrie, O. S. Binbrek, M. Strauss and I. P. Swainson, *J. Solid State Chem.*, 2002, **166**, 415-420.
47. D. R. Allan, S. J. Clark, M. J. P. Brugmans, G. J. Ackland and W. L. Vos, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1998, **58**, R11809-R11812.
48. A. R. Choudhury, K. Islam, M. T. Kirchner, G. Mehta and T. N. Guru Row, *J. Am. Chem. Soc.*, 2004, **126**, 12274-12275.
49. D. Pinkowicz, K. Kurpiewska, K. Lewinski, M. Balanda, M. Mihalik, M. Zentkova and B. Sieklucka, *CrystEngComm*, 2012, **14**, 5224-5229.
50. F. P. A. Fabbiani, D. C. Levendis, G. Buth, W. F. Kuhs, N. Shankland and H. Sowa, *CrystEngComm*, 2010, **12**, 2354-2360.

Author Biographies

Rachael Lee was born in Hartlepool, UK in 1989. Deciding to remain a Northeast England local she obtained her M.Chem. degree from Newcastle University in 2012 and then made the long and arduous journey 16 miles down the road to Durham University as a Ph.D. candidate in the groups of Jonathan W. Steed and Michael R. Probert. Her research interests are geared towards inorganic and supramolecular chemistry, single crystal X-ray diffraction and high pressure crystallography.

Judith A. K. Howard has enjoyed a long and distinguished academic career, resulting in over 1100 publications and a number of awards, including a CBE for services to science (1996), the RSC Prize for Structural Chemistry (1998) and an EPSRC Senior Fellowship (1998-2003). She was elected to the Fellowship of the Royal Society in 2002. She has pioneered new techniques in cryo-crystallography, CCD detectors, high pressure crystallography and rotating anode sources. She initiated the development of the Helix open flow low temperature system and her group have created modern crystallographic software available as the open source program, Olex2.

Michael R. Probert graduated from the University of Oxford in 2001 and carried out his Ph.D. at Durham University with Judith Howard. He remained in Durham as a Research Associate developing new experimental instrumentation for high pressure and low temperature crystallography. In 2013 he took up a position as Lecturer in crystallography at Newcastle University. His research focuses on the study of molecular systems under extreme conditions, ranging from simple organic compounds that exist as liquids under ambient conditions, to complex layered systems that undergo novel electronic and magnetic phase changes upon cooling or pressurising.

Jonathan W. Steed obtained his Ph.D. from University College London in 1993, working on organometallic chemistry. After a NATO postdoctoral fellowship at the University of Missouri he joined Kings College London in 1995. In 2004 he joined Durham University where he is currently Professor of Inorganic Chemistry. Steed is co-author of the textbook *Supramolecular Chemistry* (2009) and editor of a number of reference works. He is the recipient of Durham's Vice Chancellor's Award for Excellence in Postgraduate Teaching (2006) and the RSC Corday-Morgan Prize (2010). His interests are in solid state and pharmaceutical materials chemistry, supramolecular gels and crystal engineering.

Table of Contents Entry

This tutorial review summarises the current state of the art in low temperature and high pressure crystallography of molecualr organic and coordination compounds.